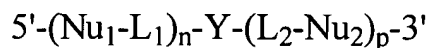


In the Claims:

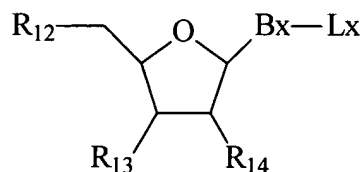
Please amend the claims as follows:

23. (Twice Amended) An oligomeric compound of the formula:



wherein:

each Nu₁ and Nu₂, independently, has the formula:



wherein

Bx is a heterocyclic base moiety;

Lx is hydrogen, a protecting group or a substituent group;

one of R₁₂, R₁₃ and R₁₄ is hydroxyl, a protected hydroxyl, a covalent attachment to a solid support, a nucleoside, an oligonucleoside, a nucleotide, an oligonucleotide, a conjugate group or an optionally protected substituent group;

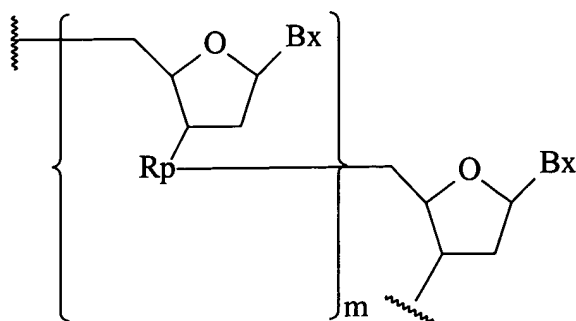
another of R₁₂, R₁₃ and R₁₄ is hydrogen, hydroxyl, a protected hydroxyl or an optionally protected substituent group;

the remaining of R₁₂, R₁₃ and R₁₄, of Nu₁, is L₁;

the remaining of R₁₂, R₁₃ and R₁₄, of Nu₂, is L₂;

each L₁ and each L₂ is, independently, a phosphodiester internucleoside linkage or a modified internucleoside linkage;

Y has the formula:



wherein:

each R_p is a chiral R_p phosphorothioate internucleotide linkage; and

each n , m and p , independently, is at least 1; where the sum of n , m and p is from 4 to about 49;

with the proviso that at least one of R_{12} , R_{13} , R_{14} and L_x is a substituent group or at least one of L_1 and L_2 is a modified internucleoside linkage,

wherein the oligomeric compound comprises from 5 to about 50 nucleosides.

Please cancel claims 37 and 40-43, without prejudice.

REMARKS

The Advisory Action indicates that Applicants' amendments filed on March 11, 2003, have been entered, thus leaving claims 23-43 pending in the instant application. Upon entry of the foregoing amendments, however, claims 23-36 and 38-39 will be pending in the instant application. Support for the foregoing amendments can be found in Applicants' specification at, for example, page 28, lines 10-15. No new matter has been added.

In view of the remarks to follow, Applicants request that the rejections of record be reconsidered and withdrawn.

Foremost, Applicant would like to thank Examiner Owens for the opportunity of telephonic interviews conducted on May 14, 2003, and June 9, 2003. Applicants appreciate the time that Examiner Owens took out of his schedule to discuss the present application with the undersigned. Applicants understand the Examiner's position to be that the claims read on any prior art showing two nucleosides linked by a chiral region. Although Applicants respectfully disagree with such position, Applicants have amended independent claim 23 to advance prosecution of the instant patent application. Specifically, Applicants have amended independent claim 23 to further recite that the gapmers defined therein comprise *from 5 to about 50 nucleosides*.

Obvious-Type Double Patenting

Since it is not clear from the Advisory Action whether Applicants' arguments filed on March 11, 2003, were sufficient to overcome the double patenting rejection, Applicants restate their position with respect to such rejections.

Claims 23-43 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 9 of commonly owned U.S. Patent No. 5,852,188 to Cook ("the Cook patent"). Applicants respectfully traverse this rejection.

An obviousness-type double patenting rejection is "analogous to [a failure to meet] the non-obvious requirement of 35 U.S.C. § 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (CCPA 1967); MPEP § 804 at 800-22. The analysis employed in an obviousness-type double patenting rejection must satisfy the same standards applicable to a rejection under §

103, except that only the claims of the earlier patent (rather than the disclosure) may be used as prior art. *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Vogel*, 422 F.2d 438, 441-42 (C.C.P.A. 1970); MPEP § 804 at 800-22. Such analysis requires, among other things, a determination of the scope and content of the pertinent prior art and an identification of the differences between it and the claims at issue. *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 989, 991 (Fed. Cir. 1988). Moreover, to establish a *prima facie* case of obviousness, “there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant.” *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998).

Significantly, the Office Action fails to provide any evidence or technical reasoning indicating that those of ordinary skill in the art would have been motivated to modify the teachings provided by claim 9 of the Cook patent, much less modify its teachings in a way that would have produced a claimed invention. For example, the present claims are directed to *gapped* oligomeric compounds comprising *from 5 to about 50 nucleosides* wherein *an internal region linked by chiral Rp phosphorothioate 2'-deoxynucleosides is flanked by two external regions of the recited formula*. By contrast, claim 9 of the Cook patent does not specify such a structure. Rather, claim 9, which depends from claims 1 and 2, recites:

An oligonucleotide comprising a plurality of nucleoside units linked together via phosphate linkages, wherein:

at least one of the nucleoside units is a non-naturally occurring nucleoside unit; and

at least two of the nucleoside units are linked via chiral phosphate linkages (**from claim 1**),

wherein said chiral phosphate linkages are selected from the group consisting of chiral Sp phosphorothioate, chiral Rp phosphorothioate, chiral Sp alkylphosphonate, chiral Rp

alkylphosphonate, chiral Sp phosphoamidate, chiral Rp phosphoamidate, chiral Sp chiral phosphotriester or chiral Rp phosphotriester (**from claim 2**); and

wherein the oligonucleotide forms at least a portion of a preselected RNA or DNA sequence (**from claim 9**).

Thus, claim 9 makes no mention of the claimed *gapped* oligomeric compounds. Although the claim requires that at least two of the nucleoside units be “linked via chiral phosphate linkages,” it does not teach or suggest that such linkages link 2'-deoxynucleosides, or that the chiral phosphate linkages be located in an internal region.

Moreover, there is no evidence of record indicating that those skilled in the art would have been motivated to modify the subject matter of claim 9 of the Cook patent in a way that would have produced one of Applicants' claimed gapped oligonucleotide compounds. In view of these deficiencies, Applicants respectfully request the rejection based upon obviousness-type double patenting be reconsidered and withdrawn.

The Advisory Action

Applicants' claimed inventions relate to *gapped* oligomeric compounds (“gapmers”) comprising a plurality of covalently-bound nucleosides wherein the oligomeric compound has an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides flanked on each end by external regions, wherein the external regions impart nuclease resistance to the oligomeric compound. The claimed gapmers are defined by the three distinct regions illustrated by the formula 5'-(Nu₁-L₁)_n-Y-(L₂-Nu₂)_p-3', as defined by claim 23, for example. As explained above, Applicants have amended independent claim 23 to further recite that the gapmers defined therein comprise *from 5 to about 50 nucleosides*.

In the Advisory Action, the Examiner alleges that, throughout prosecution, Applicants have not specifically responded as to *why* the definition of the three claimed regions is not set forth in the prior art. Applicants, however, respectfully disagree as the record is replete with argument as to *why* the prior art does not set forth Applicants' claimed invention. Accordingly, Applicants will reiterate their position with respect to the art of record in view of the foregoing amendments.

Rejection Under 35 U.S.C. § 102(b)

1. *U.S. Patent No. 5,883,237 to Stec et al. ("the Stec patent")*

Claims 23-43 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the Stec patent. Applicants respectfully traverse this rejection because the Stec patent does not disclose each and every element of the claimed inventions. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ.2d 1051, 1053 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.").

Applicants' claimed inventions relate to ***gapped*** oligomeric compounds ("gapmers") that have, *inter alia*, an internal chiral Rp deoxyphosphorothioate region flanked on each end by external regions. Significantly, as amended above, the claimed gapmers comprise ***from 5 to about 50 nucleosides***.

The Stec patent, in contrast, does not disclose gapmers comprising ***from 5 to about 50 nucleosides***, let alone the three-region gapmers having an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external flanking regions as defined by

Applicants' claimed invention. Rather, the Stec patent merely discloses solid phase synthesis of a polymer having a predetermined sequence of R_p or S_p linkages (*see, e.g.*, col. 2, lines 56-61). Nowhere does the Stec patent teach an oligonucleotide having **3 regions**: (1) an internal region of R_p chiral phosphorothioate linkages as defined in Applicants' claims; and (2) & (3) two external regions, as defined in Applicants' claims, flanking the internal region. Column 7, lines 14-67 of the Stec patent confirms this: the only sequences disclosed in the cited passage of the Stec patent are either all "ps," all "pr," or alternating "ps" and "pr" linkages (col. 7 at lines 41-43). Indeed, the Stec patent's teaching of oligonucleotides having all "ps," all "pr," or alternating "ps" and "pr" linkages cannot constitute an anticipation of Applicant's claimed invention because such teaching does not disclose Applicants' claimed gapmers having an internal region of R_p chiral phosphorothioate linked 2'-deoxynucleosides and two external flanking regions. Applicants' claimed gapmers also comprise *from 5 to about 50 nucleosides*. The Stec patent, therefore, does not disclose every element of Applicants' claimed inventions. Accordingly, reconsideration and withdrawal of the rejection based upon the Stec patent is respectfully requested.

2. *U.S. Patent No. 5,506,212 to Hoke et al. ("the Hoke patent")*

Claims 23-43 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the Hoke patent. Applicants respectfully traverse this rejection because the Hoke patent does not disclose each and every claim element.

As noted above, the claims relate to gapped oligomeric compounds having an internal region of chiral Rp phosphorothioate-linked 2'-deoxynucleosides and two external flanking regions (*see, e.g.*, claim 23). Also noted above, Applicants' claimed gapmers comprise *from 5 to about 50 nucleosides*. Although the Office Action asserts that claims 2 and 4 of the Hoke patent teach the recited characteristic at columns 7-9 and claims 2 and 4 (Office Action at 3), Applicants cannot find any such teaching in the Hoke patent. Claim 2 of the Hoke patent, for example, merely recites an oligonucleotide (represented by sequence I.D. No. 4) wherein at least 75% of the nucleoside units are joined together by Rp phosphorothioate 3' to 5' linkages. Significantly, Applicants do not understand (and the Office Action does not explain) how the phrase "at least 75% of the nucleoside units are joined together by Rp phosphorothioate 3' to 5' linkages" refers to an oligonucleotide wherein the 75% Rp-linked nucleosides are adjacent to one another and flanked by two external regions as defined by Applicants' claimed invention. Accordingly, reconsideration and withdrawal of the reject based upon the Hoke patent is respectfully requested.

3. *U.S. Patent No. 5,852,188 to Cook ("the Cook patent")*

Claims 23-43 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the Cook patent. Applicants respectfully traverse this rejection because the Cook patent does

not disclose each and every claim element.¹ The Cook patent, for example, does not disclose an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region wherein the gapmer comprises *from 5 to about 50 nucleosides*. Although the Office Action asserts that the Cook patent teaches the recited characteristic at column 5, line 45 to column 7 (Office Action at 3-4), Applicants note that no such teaching is present in the Cook patent. Rather, the Cook patent discloses sequence-specific oligonucleotides having either *substantially pure* or *pure* chiral Sp phosphorothioate, chiral Rp phosphorothioate, chiral Sp alkylphosphonate, chiral Rp alkylphosphonate, chiral Sp phosphoamidate, chiral Rp phosphoamidate, chiral Sp phosphotriester, and chiral Rp phosphotriester linkages (*see, e.g.*, col. 5, lines 46-67). Significantly, Applicants do not understand (and the Office Action does not explain) how such a general list of potential linkages could disclose an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region.

The Office Action at page 4 relies on Applicants' *specification* for the purported teaching at page 27, lines 30-35, that "any compound [can be] connected to either side of the chiral phosphorothioate." However, *no such teaching* appears at page 27, lines 30-35, nor is it seen how such would be relevant to the instant rejection even if it did.

Although the Office Action attempts to arbitrarily define internal and external regions within the oligonucleotides disclosed in the Cook patent for the purpose of alleging that such

¹ Although the instant rejection is a rejection under 35 U.S.C. § 102(b), the Cook patent is *not* available as prior art against the instant application under 35 U.S.C. § 102(b). In particular, the instant application has a filing date of November 12, 1999, whereas the Cook patent became available to the public on December 12, 1998, less than one year before the instant application was filed. Accordingly, the Cook patent is not a 35 U.S.C. § 102(b) reference.

regions correspond to those recited in Applicants' claims, the Cook patent simply does not disclose the claimed structure. The Office Action, for example, has not even indicated where the transitions lie between the alleged internal and external regions of the oligonucleotides disclosed in the Cook patent. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) based upon the Cook patent is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 23-42 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Cook patent in combination with U.S. Patent No. 5,532,130 to Alul ("the Alul patent"). Applicants respectfully request that this rejection be withdrawn, as there is no evidence of record indicating that those of ordinary skill would have been motivated to combine the teachings of the Cook and the Alul patents or even that such combination would have resulted in one of Applicants' claimed inventions. As discussed above for example, the Cook patent does not disclose "an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region" as recited by Applicants' claims. The Alul patent does not remedy this deficiency, nor has it been alleged to do so. Thus, combination of the Cook and Alul patents would not have resulted in any claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully requested.